Autoimmune Ganglionic Blockade. A Cause of Autonomic Failure.
Focus on “Experimental Autoimmune Autonomic Neuropathy”

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If we are seeking evidence about the importance of the autonomic nervous system in daily life, we need only witness the disabling nature of autonomic disorders. Patients with severe autonomic failure are unable to stand but for few seconds, before syncope ensues due to orthostatic hypotension. The autonomic nervous system modulates the function of virtually all organ systems; thus these patients also suffer a myriad of other symptoms. Most cases of autonomic failure progress slowly due to neurodegenerative processes or systemic illnesses. Some cases have a subacute onset in association with viral illnesses or paraneoplastic syndromes. In its severest form, previously normal individuals can develop complete autonomic failure and be bedridden within a few days.

It has been suspected that these subacute forms of autonomic failure have an autoimmune pathogenesis. Until recently, however, the endogenous antigen against which the autoantibodies were directed was not known. Potential candidates would have to explain the combined involvement of both sympathetic and parasympathetic systems observed clinically. In this regard, the autonomic ganglia seemed an attractive candidate; both sympathetic and parasympathetic pathways share ganglionic acetylcholine neurotransmission involving \( \alpha_4 \) nicotinic receptors, and blockade of these receptors leads to transient autonomic failure (Jordan et al. 1998). It seemed possible, therefore, that antibodies against ganglionic nicotinic receptors would produce autonomic disorders. Indeed, antibodies against ganglionic nicotinic receptors have been found in 30% of patients with paraneoplastic neuropathy and 50% of patients with acute pandysautonomia (Vernino et al. 1998, 2000).

In humans, 16 different subunits of nicotinic receptors have been identified (\( \alpha_1–7, \alpha_9–10, \beta_1–4, \delta, \epsilon, \) and \( \gamma \)), and pentameric receptors are formed by various combinations of these subunits. The nicotinic receptors that mediate autonomic ganglia neurotransmission (\( \alpha_4 \)) are structurally similar to nicotinic receptors that mediate neuromuscular transmission (\( \alpha_7 \)), but the latter contain \( \alpha_1 \) subunits and the former \( \alpha_3 \) subunits. Mice lacking the \( \alpha_3 \) subunit of the nicotinic acetylcholine receptor are characterized by neurogenic bladder and mydriasis unresponsive to light (Xu et al. 1999), obvious signs of autonomic impairment. It seemed logical, therefore, to investigate if antibodies against \( \alpha_3 \) subunits of the \( \alpha_4 \) receptor would lead to autoimmune autonomic disorders. Accordingly, Lennon et al. (2003) immunized rabbits with recombinant \( \alpha_3 \) subunit and found that animals developed features of severe autonomic neuropathy, with profound gastrointestinal hypomotility, dilated pupils with impaired light response, and grossly distended bladders. Inferior mesenteric ganglion neurons were present, but neurotransmission was impaired, confirming a postsynaptic channelopathy. In addition, ganglionic nicotinic receptor protein was found in small-cell carcinoma lines, identifying this cancer as a potential initiator of ganglionic nicotinic receptor autoimmune.

In this issue, Vernino and colleagues 2003 (pgs. 2053–2059) report the autonomic cardiovascular alterations observed in this animal model. Animals had decreased food intake, probably reflecting gastrointestinal autonomic abnormalities. This lead to profound weight loss, which could nonspecifically impact autonomic function. The authors used food-restricted controls to account for this weight loss and showed convincingly that immunized rabbits have both sympathetic and parasympathetic failure. Animals had decreased heart rate variability, suggesting cardiac vagal impairment, and decreased plasma levels of norepinephrine and its intraneuronal metabolite dihydroxyphe- nylglycol, suggesting sympathetic impairment. Low frequency variability of blood pressure also could have been used to demonstrate sympathetic impairment, replicating findings in patients with idiopathic autonomic failure and ganglionic-blocked normal controls (Diedrich et al. 2003).

This finding is an important contribution in many regards. It shows that antibodies can induce autonomic neuropathy that resembles the human disease, providing proof-of-concept for autoimmune autonomic neuropathies. Vernino et al. (2000) also found that antibody titer levels correlate with the severity of the disease, suggesting that antibody titers can be used to predict prognosis or guide treatment. Ultimately, one would hope that antigen-specific therapy will be developed for autoimmune autonomic disorders, like those being developed for myasthenia gravis (Drachman 2003). Finally, this and similar animal models will be useful in autonomic research, to clarify the role of the autonomic nervous system in physiological processes or, conversely, to eliminate the confounding effect of autonomic reflexes. A similar approach, using the ganglionic blocker trimethaphan, has proven useful in humans (Diedrich et al. 2002).

REFERENCES


